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Original Article

Potential of fenugreek (*Trigonella foenum-graecum* L.) metabolites as dental residual ridge resorption inhibitors through estrogen receptor signaling: *In silico* study

[Potencial de metabolitos del fenogreco (*Trigonella foenum-graecum* L.) como inhibidores de la resorción de la cresta residual dental a través de la señalización del receptor de estrógenos: Estudio *in silico*]

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Abstract

Context: Edentulism is a global health burden with long-life disabilities. Dental implant procedures are frequently constrained to alveolar residual ridge resorption. The resorption is strongly correlated with an imbalance of osteoblast-osteoclast activities. Estrogen well established maintain bone homeostasis. Fenugreek (*Trigonella foenum-graecum* L.) is a promising drug candidate to promote estrogenic activity and resist residual ridge resorption.

Aims: To evaluate the drug-likeness, pharmacokinetic, toxicity as well as molecular interaction prediction between *T. foenum-graecum* metabolite compounds and estrogen receptor-α (ESRα)/estrogen receptor-ß (ESRß).

Methods: The drug-likeness was evaluated using Lipinski's rule of five. A web server (PkCSM) was used to predict the pharmacokinetics and toxicity. The metabolites were retrieved from the Kanaya database. The biological activity prediction was performed using PASS Online. The ligands' structures were downloaded from PubChem National Centre for Biotechnology Information database. Proteins were obtained from Protein Data Bank. Molecular docking prediction was carried out using PyRx software and visualized using Discovery Studio Software.

Results: Quercetin, naringenin, luteolin, and kaempferol displayed the highest biological activity of estrogen agonist, anti-inflammatory, and tumor necrosis factor (TNF) expression inhibitor. Four metabolites exhibited the potential to be developed as oral drugs with good absorption in gastrointestinal, moderate tissue distribution, and safe for liver tissue. Quercetin and kaempferol showed the most negative value of binding affinity. Quercetin formed three hydrogen bonds and eight hydrophobic bonds with ESRα. Luteolin had three hydrogen bonds and five hydrophobic bonds on ESRβ.

Conclusions: Metabolites present in *T. foenum-graecum,* like quercetin, naringenin, luteolin, and kaempferol, were potential drug candidates that could act as estrogen agonists to inhibit the dental residual ridge resorption.

Keywords: dental; estrogen; fenugreek; resorption.

Resumen

Contexto: El edentualismo es una carga sanitaria mundial con discapacidades de larga duración. Los procedimientos de implantes dentales se ven frecuentemente limitados por la reabsorción de la cresta alveolar residual. La reabsorción está fuertemente correlacionada con un desequilibrio de las actividades de los osteoblastos-osteoclastos. Los estrógenos bien establecidos mantienen la homeostasis ósea. El fenogreco (*Trigonella foenum-graecum* L.) es un fármaco candidato prometedor para promover la actividad estrogénica y resistir la reabsorción residual de la cresta.

Objetivos: Evaluar la similitud farmacológica, farmacocinética, toxicidad, así como la predicción de interacción molecular entre los compuestos metabolitos de *T. foenum-graecum* y el receptor de estrógeno-α (ESRα)/receptor de estrógeno-ß (ESRß).

Métodos: La similitud con el fármaco se evaluó mediante la regla de los cinco de Lipinski. Se utilizó un servidor web (PkCSM) para predecir la farmacocinética y la toxicidad. Los metabolitos se recuperaron de la base de datos Kanaya. La predicción de la actividad biológica se realizó con PASS Online. Las estructuras de los ligandos se descargaron de la base de datos PubChem del Centro Nacional de Información Biotecnológica. Las proteínas se obtuvieron del Protein Data Bank. La predicción del acoplamiento molecular se llevó a cabo con el software PyRx y se visualizó con el software Discovery Studio.

Resultados: Quercetina, naringenina, luteolina y kaempferol mostraron la mayor actividad biológica como agonistas estrogénicos, antiinflamatorios e inhibidores de la expresión del factor de necrosis tumoral (TNF). Cuatro metabolitos mostraron el potencial para ser desarrollados como fármacos orales con buena absorción gastrointestinal, distribución tisular moderada y seguros para el tejido hepático. Quercetina y kaempferol mostraron el valor más negativo de afinidad de unión. Quercetina formó tres enlaces de hidrógeno y ocho enlaces hidrofóbicos con ESRα. Luteolina tenía tres enlaces de hidrógeno y cinco enlaces hidrofóbicos con ESRβ.

Conclusiones: Los metabolitos presentes en *T. foenum-graecum*, como quercetina, naringenina, luteolina y kaempferol, fueron potenciales candidatos a fármacos que podrían actuar como agonistas de estrógenos para inhibir la reabsorción de la cresta residual dental.

Palabras Clave: dental; estrógeno; fenogreco; reabsorción.

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INTRODUCTION

Edentulism is defined as an oral condition without natural teeth. Edentulism is highly prevalent in the global population. Both partial and complete edentulism would decrease the quality of life because of disruption of the mechanical mastication process, speech difficulties, and poor aesthetic performance (Al-Rafee, 2020). Older people are more susceptible to edentulism than young. Other edentulism-associated factors were lower education, lifestyle, smoking, and systemic diseases. Therefore, edentulism is rising as a public health problem that needs to be controlled (Tyrovolas et al., 2016).

A dental implant provides better prognostic for edentulism cases. Alveolar residual ridge is crucial for conventional implant placement procedures. The limited residual ridge position and inclination would be challenging for further dental implants (Alshenaiber et al., 2021). Buccolingual alveolar bone drastically decreases in height following tooth extraction. The percentage of decrement increases in a time-dependent manner, approximately after 3-6 months post extraction (Tan et al., 2012). Clinical observation found unidirectional structural changes in the edentulous jawbone. Osteoclast is predominant and invokes the resorption of rest alveolar bone. Bone remodeling associated with osteoclast activity resorbs the pit of the external alveolar surface. The inequilibrium with osteoblast activity results in loss of bone structure (Kondo et al., 2023).

Bone remodeling can be interrupted by the presence of estrogen. Estrogen inhibits bone resorption primarily through direct effects on osteoclasts. Conversely, estrogen affects osteoblast/osteocyte and T-cell regulation on osteoclasts. Estrogen insufficiency generates a gap between bone resorption and bone production. A molecular study found estrogen reduces osteoblast apoptosis, oxidative stress, and osteoblastic nuclear factor (NF)-κB activity (Khosla et al., 2012). Estrogen modified the ratio of pro-inflammatory and anti-inflammatory mediators. The homeostasis imbalance leads to persistent inflammation, thereby inducing tissue damage and impaired angiogenesis. Disturbance of angiogenesis resulted in a delay of wound healing and new bone development. Therefore, scar tissue and resorption are more predominant than new bone formation (Loi et al., 2016). This indicates the importance of estrogen replacement therapy to support osteogenesis and inhibit the bone resorption process.

Fenugreek (*Trigonella foenum-graecum* L., family *Leguminosae*) was previously used as a traditional medicine worldwide, particularly in Asia and the Mediterranean. The ethnomedical properties of *T. foenum-graecum* were reviewed as joint-bone pain (arthralgia) alleviation (Bahmani et al., 2016). Further scientific work demonstrated the benefit of *T. foenum-graecum* to increase the cortical bone thickness among ovariectomized animals. As ovariectomy-induced estrogen deficiency, *T. foenum-graecum* was proposed as a phytopharmaceutical for estrogen replacement therapy. However, the specific molecular mechanism has not been elucidated (Anjaneyulu et al., 2018).

The *T. foenum-graecum* metabolite compounds have been identified as alkaloids (trigonelline), steroidal sapogenins (yamogenin and diosgenin), polysaccharides (galactomannan), amino acids (4-hydroxy isoleucine), and flavonoids (quercetin) in seeds and leaves. However, the estrogenic potential of each compound remains uncertain, therefore arising the need for future evaluation (Bahmani et al., 2016).

Currently, drug candidate evaluation involves computational-aid approaches using *in silico* study. The *in silico* study is important to generate the rational use of animals in cost-effective research. The pharmacokinetics, metabolism, and toxicity prediction of drug candidates are well described using computational-aid approaches (Brogi et al., 2020). Thus, this study aimed to evaluate the potential of *T. foenum-graecum* to inhibit dental residual ridge resorption via estrogen receptor signaling by *in silico* study. This study comprehensively evaluated the drug-likeness, pharmacokinetic, metabolism, toxicity, and molecular interaction prediction of *T. foenum-graecum* metabolite compounds as inhibitors of dental residual alveolar ridge resorption by modulation in estrogen receptor molecules.

MATERIAL AND METHODS

Data mining, ligand, and protein preparation

The protein of ESR- α (1X7R) and ESR-β (5TOA) were retrieved from Protein Data Bank (https://www.rcsb.org/) as PDB format. The previously attached water molecules on the protein were removed using Discovery Studio 2019 software. The metabolite compounds of *T. foenum-graecum* were obtained from Kanaya KnapSack database (Nakamura et al., 2013). The 3D structures of ligands were downloaded in SDF format from PubChem (https://pubchem.ncbi.nlm.nih.gov/). Genistein and estradiol were used for control ligands (Yuseran et al., 2019). The ligands were energy minimized and converted into PDB format using the Open Babel software in PyRx v.0.9.9 (Dallakyan and Olson, 2015).

Biological activity analysis

The screening of biological activity was predicted using PASS Online (http://www.way2drug.com/PASSOnline/). The probability to be active (Pa) score (range 0-1) is a prediction score from PASS Online to describe the activity potential of a compound. The closer to value 1, the stronger the prediction. The cut-off used in this study was Pa>0.5 (Filimonov et al., 2014).

Drug-likeness, pharmacokinetic and toxicity prediction

Lipinski's rule of five was performed to predict the drug-likeness of selected metabolite compounds of *T. foenum-graecum* using a free accessible website. The predicted absorption, distribution, metabolism, and toxicity profiles were analyzed using the pKcsm program at http://biosig.unimelb.edu.au/pkcsm (Utami et al., 2022).

Molecular docking analysis, validation, and visualization

Molecular interaction prediction was performed using Autodock Vina integrated into PyRx v.0.9.9. Docking was carried out using the targeted docking method with an exhaust parameter of 25. The grid box size was adjusted to the position of the protein amino acid residues bound to the experimental control. For ESRα, the grid box was set as follows: Center X: 15.1459833174, Y: 31.1794651394, Z: 21.8784262334, and dimensions (Å) X: 20, Y: 20, Z: 20. While the grid box settings for ESRβ were as follows: Center X: 19.7414220736, Y: 42.8083137782, Z: 15.8294390702, and dimensions (Å) X: 23.5813501083, Y: 22.8862644419, and Z: 21.6996053098. The docking was validated using the root mean square deviation (RMSD) value. The RMSD ≤ 2 Å was set as a validation value of protein-ligand interaction. The interaction binding was visualized using BioVia Discovery Studio 2019 software (Utami et al., 2022).

Data analysis

The drug-likeness of Lipinski rules was categorized for better oral route drug candidates based on the following criteria: molecular weight <500, number of hydrogen bond acceptors <10, number of hydrogen bond donors <5 and the logP value less than 5. The category of poor absorption was described as a percentage less than 30%. The circulatory distribution was considered relatively low when the VDss is lower than 0.71 L kg^{-1} (log VDss <-0.15) and higher when the VDss is more than 2.81 L kg^{-1} (log VDss >0.45). Acute toxicity prediction was interpreted as the amount of compound in a single application that caused the death of 50% of a group of test animals. Chronic toxicity prediction was represented as the highest dose with no adverse effect in tested animals (Kurnianingsih et al., 2022; Pires et al., 2015).

RESULTS AND DISCUSSION

According to database mining, in *Trigonella foenum-graecum*, 28 metabolite compounds were identified, which showed less than 500 Daltons of molecular weight. Biological activity analysis found the metabolite of quercetin, naringenin, luteolin, and kaempferol predicted as estrogen agonists according to their high scores of predicted potential activity (Pa). i.e., 0.51, 0.73, 0.56, and 0.51, respectively. Interestingly, those 4 metabolite compounds also have high Pa score activity as anti-inflammatory and TNF expression inhibitors (Table 1). The activation of estrogen receptors is essential for bone homeostasis between osteoclast and osteoblast maturation. Estrogen receptors are members of the nuclear receptor superfamily, which are involved in the recruitment of transcription factors during gene expression. Estrogen receptor-α (ESRα) and ESRß are expressed in bone tissue. Knockout of ERs gene alters the osteoblast maturation and reduces bone mass (Emmanuelle et al., 2021), and residual ridge resorption linked to inflammatory cytokine signaling such as interleukin-6 (IL-6) and tumor necrosis alpha-α (TNF-α). Previous research explained the range of bone loss as the impact of small resorption areas in periodontitis cases (Gupta et al., 2019). This indicates that *Trigonella foenum-graecum* metabolite compounds could potentially inhibit dental residual ridge resorption.

Table 2 demonstrates that quercetin, naringenin, luteolin, and kaempferol meet the Lipinski rule of five criteria thus predicted good availability as oral drug candidates. Lipinski rule of five is used to predict the oral drug-likeness of the selected compounds based on their molecular weight, log P (<5), number of hydrogen bond acceptors (≤10), and hydrogen bond donors (≤5) (Utami et al., 2022). Quercetin, naringenin, luteolin, and kaempferol have a molecular weight less than 500. The number of hydrogen bond donors was 5, 3, 4, and 5 for quercetin, naringenin, luteolin, and kaempferol, respectively. The number of hydrogen bond acceptors was 7, 5, 6, and 7 for them, respectively. All four compounds show positive log P values that indicate the compound has a higher affinity in the lipid phase (Pires et al., 2015).

The pharmacokinetic profiles show naringenin and luteolin have higher absorption in the gastrointestinal tract than quercetin and kaempferol. The gastrointestinal absorption is classified as low at less than 30%. A percentage higher than 70% indicates high absorption in the gastrointestinal tract.

Table 1. *Trigonella foenum-graecum* metabolite compounds.

C_ID	CAS_ID	Metabolite	Molecular formula	Molecular weight	Estrogen agonist (Pa)	Anti-inflammatory (Pa)	TNF expression inhibitor (Pa)
C00004631	117-39-5	Quercetin	$C_{15}H_{10}O_7$	302.04	0.51*	0.69*	0.50*
C00003597	512-06-1	Yamogenin	$C_{27}H_{42}O_3$	414.31	0.00	0.00	0.25
C00001110	3681-93-4	Vitexin	$C_{21}H_{20}O_{10}$	432.11	0.21	0.77*	0.00
C00001555	535-83-1	Trigonelline	$C_7H_7NO_2$	137.05	0.00	0.61*	0.34
C00013329	520-32-1	Tricin	$C_{17}H_{14}O_7$	330.07	0.33	0.69*	0.63*
C00003593	77-60-1	Tigogenin	$C_{27}H_{44}O_3$	416.33	0.24	0.71*	0.00
C00003592	126-18-1	Smilagenin	$C_{27}H_{44}O_3$	416.33	0.24	0.71*	0.00
C00002499	92-61-5	Scopoletin	$C_{10}H_8O_4$	192.04	0.21	0.63*	0.54*
C00034219	7432-28-2	Schisandrol A	$C_{24}H_{32}O_7$	432.21	0.14	0.55*	0.42
C00002904	155-58-8	Rhaponticin	$C_{21}H_{24}O_9$	420.14	0.20	0.65*	0.40
C00005374	522-12-3	Quercetin 3-O-L-rhamnoside	$C_{21}H_{20}O_{11}$	448.10	0.36	0.75*	0.23
C00001078	28608-75-5	Orientin	$C_{21}H_{20}O_{11}$	448.10	0.20	0.63*	0.35
C00057400	470-01-9	Neotigogenin	$C_{27}H_{44}O_3$	416.33	0.24	0.71*	0.00
C00000982	480-41-1	Naringenin	$C_{15}H_{12}O_5$	272.07	0.73*	0.66*	0.50*
C00000674	491-70-3	Luteolin	$C_{15}H_{10}O_6$	286.05	0.56*	0.66*	0.64*
C00004565	520-18-3	Kaempferol	$C_{15}H_{10}O_6$	286.05	0.51*	0.69*	0.48
C00001059	38953-85-4	Isovitexin	$C_{21}H_{20}O_{10}$	432.11	0.19	0.47	0.33
C00004635	480-19-3	Isorhamnetin	$C_{16}H_{12}O_7$	316.06	0.42	0.66*	0.56*
C00001055	4261-42-1	Isoorientin	$C_{21}H_{20}O_{11}$	448.10	0.16	0.49	0.34
C00002647	149-91-7	Gallic acid	$C_7H_6O_5$	170.02	0.11	0.55*	0.56*
C00002525	485-72-3	Formononetin	$C_{16}H_{12}O_4$	268.07	0.48	0.52*	0.39
C00001017	578-74-5	Apigenin 7-O-beta-D-glucopyranoside	$C_{21}H_{20}O_{10}$	432.11	0.30	0.71*	0.26
C00013291	38070-97-2	7-Hydroxy-6-methoxyflavone	$C_{16}H_{12}O_4$	268.07	0.23	0.56*	0.61*
C00003800	2196-14-7	7,4'-Dihydroxyflavone	$C_{15}H_{10}O_4$	254.06	0.19	0.52*	0.54*
C00053459	14417-51-7	4-O-beta-D-Mannopyranosyl-D-mannose	$C_{12}H_{22}O_{11}$	342.12	0.00	0.54*	0.00
C00057876	14002-93-8	3,4,7-Trimethylcoumarin	$C_{12}H_{12}O_2$	188.08	0.00	0.53*	0.36
C00003825	2150-11-0	3',4',7-Trihydroxyflavone	$C_{15}H_{10}O_5$	270.05	0.00	0.00	0.39
C00003672	83-46-5	(-)-beta-Sitosterol	$C_{29}H_{50}O$	414.39	0.22	0.47	0.32

Molecular weight <500 Dalton based on Kanaya database (Nakamura et al., 2013) and the score of biological activity prediction (PASS Online).

Table. 2. The druglikeness, pharmacokinetics and toxicity prediction of Fenugreek metabolite compounds.

Metabolite	Lipinski	Water solubility (log mol/L)	Intestinal absorption (human) (%)	VDss (human) (L/kg)	CYP2D6 substrate	CYP3A4 substrate	Total clearance (mL/min/kg)	Oral rat acute toxicity (LD50) (mol/kg)	Oral rat chronic toxicity (LOAEL) (mL/kg_bw/day)	Hepato-toxicity	Skin sensiti-zation
Quercetin	Yes	-2.93	77.21	1.56	No	No	0.41	2.47	2.61	No	No
Naringenin	Yes	-3.22	91.31	-0.02	No	No	0.06	1.79	1.94	No	No
Luteolin	Yes	-3.09	81.13	1.15	No	No	0.50	2.46	2.41	No	No
Kaempferol	Yes	-2.93	77.21	1.56	No	No	0.41	2.47	2.61	No	No

The distribution of all compounds in various tissues is designated as VDss value. The tissue distribution is considered relatively low when the VDss is lower than 0.71 L kg^{-1} (log VDss <-0.15), higher distribution when the VDss is higher than 2.81 L kg^{-1} (log VDss >0.45). The range between 0.71-2.81 is considered a moderate distribution (Utami et al., 2022). Four of the candidate compounds showed moderate tissue distribution, whereas the distribution of naringenin was lower than quercetin, naringenin, and kaempferol. Those four compounds exhibited no role as CYP2D6 and CYP3A4 substrates. Therefore, the compound of naringenin, luteolin, quercetin and kaempferol were predicted pass the first drug metabolism pathway in liver tissue (Fatima et al., 2019). The kidney total clearance was highest for luteolin than others. Safety and toxicities prediction show quercetin and kaempferol showed higher acute and chronic lethal doses. However, all compounds showed no adverse toxicity on the liver and skin (Table 2).

Molecular docking interaction showed the binding affinity of *Trigonella foenum-graecum* metabolite compounds ranged from 8.8 kcal/mol to -9.0 kcal/mol. Quercetin displayed the most negative binding affinity (-9.0 kcal/mol) on ESRα compared to other compounds. The binding interaction between kaempferol and ESRβ exposed the most negative value (-9.1 kcal/mol) than quercetin, naringenin, and luteolin. However, those energy-binding affinity revealed lower values than control ligands, i.e., estradiol and genistein (Table 3). The binding affinity score predicts the binding interaction between the ligand and target molecule. The more negative score reflects the better binding interaction (Dallakyan and Olson, 2015).

Table 3. The molecular interaction score and interaction of ESR-α/ ESR-ß with *Trigonella foenum-graecum* metabolites analyzed using Pyrx 8.0.0 software and Discovery studio software.

Receptors	Ligand	Binding affinity (kcal/mol)	Hydrogen bond	Hydrophobic bond
ESR-α	Genistein	-9.0	GLU353, LEU387, ARG394, HIS524	LEU391, ALA350, PHE404, LEU525
	Estradiol	-10.7	**HIS524**, **LEU387**, **GLU353**, ARG394	ILE424, LEU384, LEU346, MET388, **ALA350**, **LEU391**, MET421
	Kaempferol	-8.8	GLY521, PHE404	ILE424, LEU384, LEU346, MET421, **LEU387**, **LEU391**, ALA350
	Luteolin	-8.9	GLU353, HIS524	**LEU391**, **ALA350**, **LEU387**, LEU384, LEU346, MET421, ILE424
	Naringenin	-8.8	**GLU353**	**LEU391**, **LEU387**, **ALA350**, MET421, ILE424, PHE404, LEU346
	Quercetin	-9.0	HIS524, GLY521, **GLU353**	MET421, LEU384, LEU346, ILE424, **ALA350**, **LEU391**, **LEU387**, **PHE404**
ESR-ß	Estradiol	-11.0	HIS475, GLY472, LEU339, GLU305, ARG346	ILE376, MET336, MET340, PHE356, LEU343, ALA302, ILE373, LEU298
	Kaempferol	-9.1	MET295, **GLU305**	LEU339, LEU298, LEU476, **LEU343**, **ALA302**
	Luteolin	-8.9	**GLY472**, MET295, **GLU305**	LEU339, **LEU343**, **PHE356**, **LEU298**, LEU476
	Naringenin	-9.0	**GLY472**	**PHE356**, **LEU343**, LEU339, **ALA302**, LEU476
	Quercetin	-8.9	**LEU339**, **GLU305**	LEU476, LEU298, MET295, **PHE356**, **LEU343**, **ALA302**

Bold letters represent amino acid interactions similar to the control (estradiol).

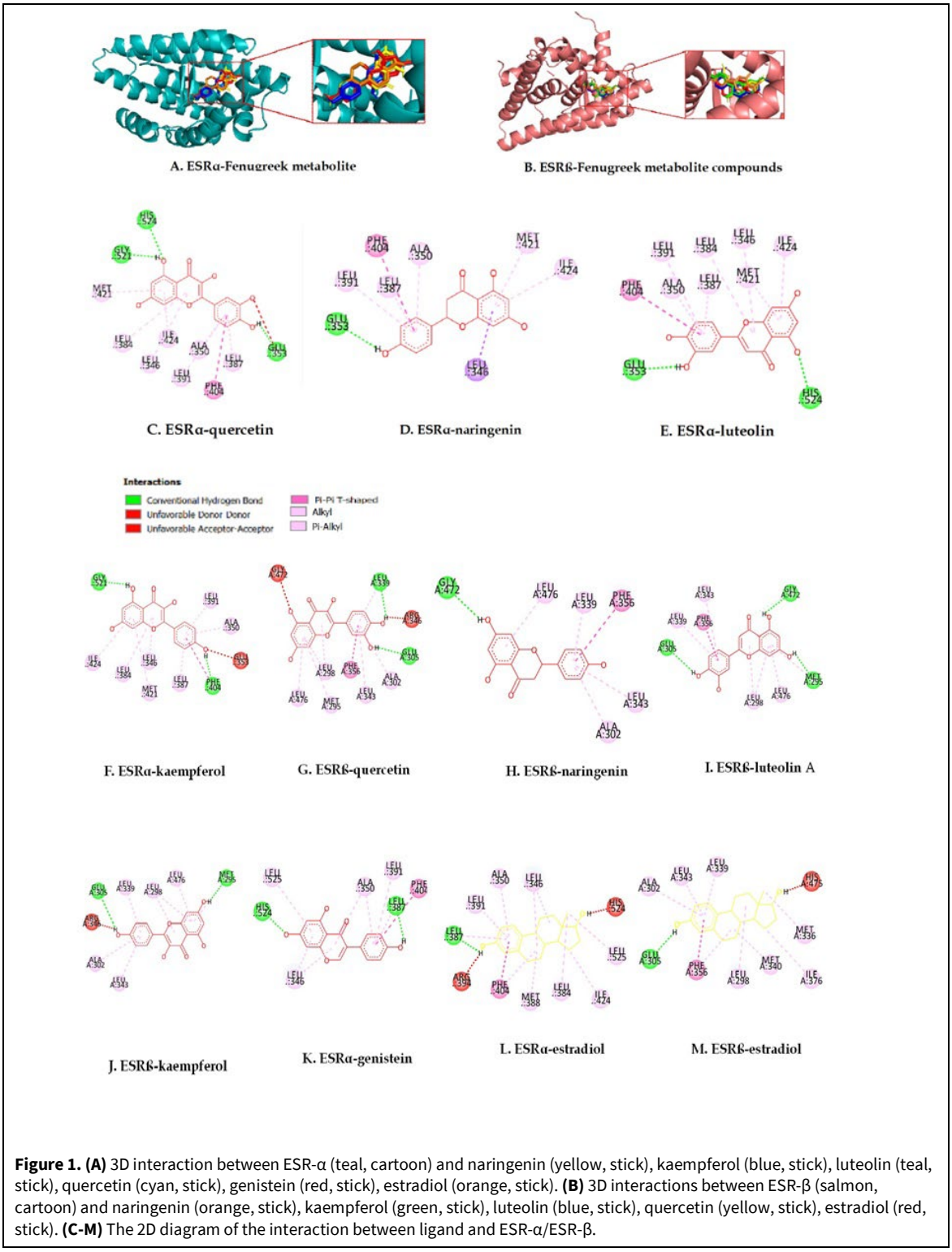

Figure 1. (A) 3D interaction between ESR-α (teal, cartoon) and naringenin (yellow, stick), kaempferol (blue, stick), luteolin (teal, stick), quercetin (cyan, stick), genistein (red, stick), estradiol (orange, stick). **(B)** 3D interactions between ESR-β (salmon, cartoon) and naringenin (orange, stick), kaempferol (green, stick), luteolin (blue, stick), quercetin (yellow, stick), estradiol (red, stick). **(C-M)** The 2D diagram of the interaction between ligand and ESR-α/ESR-β.

Among the four candidates, the interaction of quercetin-ESRα exhibited the most similar interaction with estradiol-ESRα. Quercetin formed 3 hydrogen bonds and 8 hydrophobic bonds with ESRα. The similar residues of quercetin-ESRα were recognized as hydrogen bonds at the amino residue of GLU353 and hydrophobic bonds at ALA350, LEU387, LEU391, and PHE404. Luteolin showed 3 hydrogen bonds and 5 hydrophobic bonds on ESRβ. The similar interaction site between luteolin-ESRβ and estradiol-ESRβ was identified on amino residues of GLY472, GLU305, PHE356, LEU343, and LEU298 (Fig. 1, Table 3). A greater number of amino residues indicates the interaction stabilization between protein and ligand (Senior et al., 2020).

A previous study revealed estrogen plays an essential role in resisting the inflammation following orthodontic tooth movement by reducing the expres-

sion of TNF-α, matrix metalloproteinase-2 (MMP-2) and increasing the anti-inflammatory cytokine IL-10 (Amaro et al., 2020). According to the biological activity, oral drug-likeness, potential pharmacokinetic, and safety of metabolite compounds from *T. foenum-graecum*, further studies are necessary to confirm the advanced health benefits as an inhibitor of dental residual ridge resorption.

CONCLUSION

Quercetin, naringenin, luteolin, and kaempferol contained in *Trigonella foenum-graecum* could be developed as drug candidates to inhibit residual ridge resorption through estrogen agonist signaling. Future research must reveal the molecular mechanism through more extensive *in vitro* and *in vivo* studies.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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AUTHOR CONTRIBUTION:

Contribution	Lodra EH	Effendi MC	Permatasari N	Drajat RS
Concepts or ideas	x	x	x	x
Design	x			
Definition of intellectual content	x			
Literature search	x			
Experimental studies	x			
Data acquisition	x			
Data analysis	x			
Statistical analysis	x			
Manuscript preparation	x			
Manuscript editing	x	x	x	x
Manuscript review	x	x	x	x

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